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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Paper No. 29

Serial Number: 08/014,096
Filing Date: 04 February 1993
Appellant(s): Huston et al.

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GROUP 1800

Edmund R. Pitcher
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed 20 September 1994.

(1) Status of claims.

The statement of the status of claims contained in the brief 5 is correct.

(2) Status of Amendments After Final.

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(3) Summary of invention.

10 The summary of invention contained in the brief is correct.

(4) Issues.

The appellant's statement of the issues in the brief is correct.

(5) Grouping of claims.

15 Appellant's brief includes a statement that claims 47 to 53, 56 to 61 and 63 and claims 64 to 68 do not stand or fall together and provides reasons as set forth in 37 C.F.R. § 1.192(c)(5) and (c)(6).

The appellant's statement in the brief that certain claims 20 do not stand or fall together is not agreed with because the only two independent claims, 47 and 64, are drawn to two materially identical polypeptides. All of the physical limitations of a polypeptide of claim 47 are exactly the same as the physical limitations of a polypeptide encompassed by claim 64. Any 25 argument which would be applicable to claims 47 to 53, 56 to 61

and 63 would, therefore, be equally applicable to claims 64 to 68. In fact, any rejection which is applied to claim 47 would have to be applied 64 since they are drawn to identical products. Additionally, Appellant has not identified that element which makes one group patentably distinct in view of the other and Appellant has not disclosed how that distinguishing element is lacking or unobvious in light of the prior art of record.

5 (6) Claims appealed.

The copy of the appealed claims contained in the Appendix to 10 the brief is correct.

(7) Prior Art of record.

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

U.S. Pat. No. 4,741,180, issued 14 June 1988, Cousens et al.

15 U.S. Pat. No. 4,743,679, issued 24 Feb. 1988, Cohen et al.

W.O. 84/03103, published 16 Aug. 1984, Löfdahl et al..

A.L. Lehninger, Biochemistry, 1978, Worth Publishing, pages 130-131.

20 (8) New prior art.

No new prior art has been applied in this examiner's answer.

(9) Grounds of rejection.

The following ground(s) of rejection are applicable to the appealed claims.

25 Claims 47 to 53, 56 to 61 and 63 to 68 stand rejected under 35 U.S.C. § 103 as being unpatentable over the Cousens et al.

patent (4,751,180) in view of the Cohen et al. patent (4,743,679). These claims are essentially drawn to a fusion protein containing a first "hook" region which facilitates the purification of that protein, a second "hinge" region defining a cleavage site whose cleavage is facilitated by its flexibility and a third region defining a desire "target" polypeptide.

The construction of a fusion protein consisting of a first component (a.k.a. leader sequence or "hook") which facilitates purification of that protein and a second component consisting of a desired protein or "target", in which these components are separated by a selectively cleavable site was old and well known in the art of molecular biology at the time that the instant invention was made. This is, in effect, conceded by Appellant in the text on pages 2 to 4 of the instant application and the references cited therein. The distinguishing feature of the claimed invention is the inclusion of a flexible linker ("hinge") adjacent to the cleavage site to facilitate the cleavage of that protein.

The Cousens et al. patent has been relied upon because it described the incorporation of a flexible linker ("spacer") composed of alternating serine and threonine residues between the two components of a fusion protein to facilitate the proteolytic cleavage of that protein prior to the making of the instant invention. Example I of the Cousens et al. patent, which was also present in patent application Serial Number 06/717,209 from

which this patent derives priority, clearly described the construction of a fusion protein consisting of two components separated by the "spacer" -Ser-Thr-Ser-Thr-Ser-Thr-Ser-, which is preceded by a serine protease cleavage site. Of the five fusion protein which were described in this example only those two having a proteolytic cleavage site contained "spacers" which indicates that these "spacers" were employed to facilitate cleavage of those proteins. The other three fusion proteins which were described therein contained chemical cleavage sites and no "spacers". The Cousens et al. patent shows that the incorporation of a flexible linker (a.k.a. "spacer", a.k.a. "hinge") between the two components of a fusion protein to facilitate the proteolytic cleavage of that protein was known and practiced in the art prior to the making of the instant invention.

The Cohen et.al. patent has been relied upon because the text from line 59 on column 3 to line 17 on column 4 of this patent shows that the avoidance of cysteine residues in the cleavable linker and leader peptide of a fusion protein to prevent the covalent interaction of these components with the desired "target" protein was old and well known in the art at the time of the instant invention. This text also shows that the incorporation of a Staphylococcus aureus V8 protease cleavage site into a fusion protein in which the desired protein component (target) lacked such a site to facilitate the separation of that

desired protein from the fusion protein after its purification was also well known in the art prior to the making of the instant invention. All of the elements of the claimed fusion polypeptide were known and used in the art, in the capacity claimed, prior to 5 the making of the instant invention.

An artisan would have found it prima facie obvious to have incorporated a flexible "spacer" like the one described in the Cousens et al. patent into a fusion protein which was composed of a leader sequence, a protease cleavage site and a desired 10 protein, as was well known in the art at that time, adjacent to the proteolytic cleavage site of that protein to facilitate the cleavage of that protein into its respective components after its purification by relieving any steric hinderance which might be produced by the other components of that fusion protein.
15 Further, that artisan would have found it prima facie obvious to have avoided any cysteine residues in the leader sequence of that fusion protein so that disulfide bonds would not be formed between the different components of that protein as taught by the Cohen et al. patent at that time.

20 (10) New ground of rejection.

This Examiner's Answer does not contain any new ground of rejection.

(11) Response to argument.

Appellant's position that the Cousens et.al. patent does not 25 receive benefit of the filing date of parent application Serial

Number 06/717, 209 under 35 U.S.C. § 120 is not applicable to the instant rejection. Appellant's position that this priority application can not be relied upon if it was not enabling for a subsequently patented invention has not been disputed. The 5 Cousins et.al. patent, however, is clearly entitled to receive benefit for that material which is common to both applications and which was enabling for subsequently allowed claims. The working examples of fusion proteins which are common to both of these applications have been relied upon for the pending rejections and these examples, as presented in application Serial 10 Number 06/717, 209 and without the benefit the additional material provided by the continuing application on which this patent issued, were clearly enabling for claims 12 to 15, 17 and 18 of that issued patent without the addition of new matter. There is 15 no question, therefore, that the Cousins et.al. patent should be given benefit of the filing date of parent application Serial Number 06/717, 209 as indicated in M.P.E.P. 901.02 for that material which is common to both documents and it is this common material which has been relied to support the standing rejection.

20 Appellant's position that the '209 application does not recite the terms "hinge amino acids" or "hinge" is also not disputed. That application has not been relied upon to provide these terms and issued claims 12 to 15, 17 and 18 do not employ or require these terms. The definition of a "hinge" which is 25 provided in the text from the last paragraph on page 5 through

the first paragraph on page 7 of the instant specification appears to encompass the -Ser-Thr-Ser-Thr-Ser-Thr-Ser- "spacer" which was described in Example I of the '209 application even though it was not expressly referred to as a "hinge" by Cousens et al. The fact that Cousens et al. did not call that "spacer" a "hinge" is irrelevant since it is encompassed by this term as defined by Appellant and that linker was employed to facilitate the cleavage of a fusion protein which is the same capacity as a "hinge" of the instant invention.

Appellant's opinion that the '209 application did not support an "enzymatically removable link" as recited in allowed claim 17 lacks support under 35 U.S.C. § 112, first paragraph, is rebuttable since the use of amino-peptidases and carboxy-peptidases to trim a cleaved fusion protein back to an authentic terminal residue was routinely practiced in the art at that time. However, this issue is not relevant to the rejection at hand because the '209 application has not been relied upon for this element, which is absent from the claims under consideration.

The fact that the -Ser-Thr-Ser-Thr-Ser-Thr-Ser- "spacer" of Cousens et al. was not expressly identified therein as a "hinge" has not gone unappreciated. However, the text on lines 31 to 35 in column 4 of the Cousens et al. patent expressly stated that "[t]he hinge region will have at least one amino acid and may have 20 or more amino acids, usually not more than 15 amino acids, particularly the nonpolar amino acids G, A, P, V, I, L and

the neutral polar amino acids, N, Q, S and T". Therefore, that "spacer" which was composed of alternating serine and threonine residues and which was described in the '209 application appears to be a "hinge" in accordance with either the definition provided by Cousens et al. or the definition provided by the instant application.

5 The new matter which was introduced in the Cousens et al. patent was clearly needed to support the ultimate breadth of the allowed claims. This issue is not relevant to a rejection under 10 35 U.S.C. § 103 because such a rejection can be made over a single obvious embodiment of the claimed invention. At no point has the '209 application been alleged to have disclosed the production of any and all "hinge" regions which are encompassed by the pending claims and the issued claims of the Cousens et al. 15 patent. The '209 application has been relied upon because it described a single embodiment of a "hinge" in the capacity claimed in the pending claims and this is sufficient to support an obviousness rejection under U.S.C. § 103.

In summary, the Cousens et al. patent and the '209 20 application, from which it derives benefit in part under 35 U.S.C. 120 for that patentable material which was common to both, has been relied upon because it described the production of five fusion proteins. Three of these proteins contained selective 25 chemical cleavage sites between the two components of the fusion proteins and two contained proteolytic cleavage sites. Those

three fusion proteins containing the chemical cleavage sites did not contain "spacers". The two fusion proteins containing proteolytic cleavage sites also contained "spacers" composed of alternating serine and threonine residues adjacent to those proteolytic cleavage sites. The DNA encoding these proteolytic cleavage sites and their associated linkers were synthesized de novo by Cousens et al. and were, therefore, not a convenient "off the shelf" reagent. In other words the composition of these "spacers" was intentional. Since one of ordinary skill in the art of biochemistry or molecular biology would have immediately recognized the flexible nature of a peptide linker composed of alternating serine and threonine residues in an aqueous environment that artisan would have known that the linker employed by Cousens et al. was used to facilitate the cleavage of those fusion proteins. This is further supported by the fact that these "spacers" were only employed in those proteins to be cleaved with a protease where one would expect the two components of that fusion protein to hinder access of that protease to the cleavage site whereas one would not expect such a problem with a chemical cleavage agent which is substantially smaller than a protease. This reference shows that the inclusion of a flexible "spacer" ("hinge") between the two components of a fusion protein to facilitate the cleavage of that protein with a protease had been described and practiced in the art of molecular biology prior to the making of the instant invention.

Appellant has alleged that the problem solved by the instant invention, the steric hindrance which prevents the access of a proteolytic cleavage site of a fusion protein by a protease, was unrecognized prior to the making of the instant invention. In 5 response to this allegation the Löfdahl et.al. publication (WO 84/03103, published 16 Aug. 1984), which was cited in the third paragraph on page 3 of the Background section of the instant specification, was provided because it shows that this problem had been recognized and was well known in the art prior to the 10 making of the fusion protein described in the '209 application. The text from line 2 of page 6 to the bottom of page 7 of the Löfdahl et.al. publication summarized the state of the art of fusion protein cleavage prior to the Cousens et.al. invention. This reference explicitly taught that "[o]ften it may be 15 preferred to use chemical cleaving agents [to cleave fusion proteins] because protease recognition sequences may be sterically hindered in the produced fused protein." This reference also stated that "[t]he techniques for introducing the corresponding DNA sequences coding for such cleavage susceptible peptide units 20 or residues into the DNA sequence coding for the fused protein or polypeptide are well-known per se in the art and need not be discussed in any detail herein". This reference clearly shows that an artisan such as Cousens et.al. was well aware that a protease cleavage site could be sterically unavailable in a fusion 25 protein whereas a chemical cleavage site generally was not.

Appellant has alleged that there is no factual basis for concluding that an artisan of ordinary skill in protein chemistry, and Cousens et.al. specifically, would have recognized that the serine-threonine-serine-threonine-serine- and serine-threonine-serine-linkers described in the '209 application were flexible. In response to that allegation an excerpt from an undergraduate biochemistry textbook which was originally published in 1970 (A. L. LEHNINGER, "BIOCHEMISTRY" published 1978 (fourth printing) by Worth Publishers, Inc. (N.Y.), pages 130 and 10 131) was provided. This excerpt taught that the amino acids tyrosine, cysteine, asparagine, serine, isoleucine, threonine, glutamic acid, aspartic acid, lysine, arginine and glycine are helix-destabilizing amino acids and that a polypeptide composed exclusively of one or more of these amino acids would be expected 15 to have a random form in which the flexible backbone undergoes continuous change as the result of thermal motion. Unless one accepts the premise that Cousens et.al. was completely ignorant of basic protein chemistry, one has to conclude that Cousens et.al. was well aware that the serine-threonine linkers they 20 constructed de novo were flexible and would facilitate the cleavage of an adjacent protease cleavage site by alleviating any potential steric hinderance in a fusion protein. There is no other credible explanation for the construction and use of these linkers in the capacity disclosed in the '209 application.

25 Appellant has taken the position that there was no explicit

motivation to combine a fusion protein containing the "spacer" of Cousens et al. with the teaching in the Cohen et al. patent to avoid cysteine residues in the leader sequence of a fusion protein. The text on lines 10 to 14 in column 4 of the Cohen et al. patent taught that "the elimination of cysteine residues in the leader peptide [of a fusion protein] prevents possible interactions and interferences with the obligatory formation of disulfide bridges in the active analogs" (target protein). The motivation to avoid cysteine residues in the leader peptide of any fusion protein in order to prevent the formation of disulfide bonds between that leader sequence and the desired (target) protein in that fusion protein is clear and explicit motivation. Additionally, the incorporation of a V8 protease cleavage site between the components any fusion protein which lacks such a site in its respective components to facilitate the separation of those components after purification was also an explicit motivation which was present in the prior art of record including the Cohen et al. and the Löfdahl et.al. publications.

Appellant has urged that a fusion protein of the instant invention, when considered as a whole, achieves results which would not have been obvious to an artisan of molecular biology in the absence of the instant application at the time that the instant invention was made. Appellant has not, however, identified those unobvious results. As stated above, the construction of a fusion protein containing a "hook", a "target"

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and a selectable cleavage site was old and well known in the art at the time that the instant invention was made. The only distinction between such a fusion protein and a fusion protein of the instant invention is the inclusion of a "hinge" adjacent to the cleavage site of a fusion protein of the instant invention to facilitate the proteolytic cleavage of that protein and the Cousens et al. priority '209 application shows that this additional element was known and used in the art in the capacity in which it is employed in the instant invention prior to its making.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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